UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OFCHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: **7/14/2017**

Subject: **Pymetrozine. Degradates of Concern in Drinking Water**

PC Code: 101103
Decision No.: 528651
Petition No.: None
Risk Assessment Type: Single Chemical Aggregate
TXR No.: None
MRID No.: None

DP Barcode: 440624
Registration No.: 100-912 and 100-913
Regulatory Action: Registration Review
Case No.: 7474
CAS No.: 123312-89-0
40 CFR: §180.556

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I. Introduction

Members of the pymetrozine risk assessment team and two members of the Residues of Concern Knowledgebase Subcommittee (ROCKS) met on 5/2/2017 to discuss the pymetrozine degradates of concern in drinking water.

Team Members: Doug Dotson, Krystle Yozzo, Christina Swartz

ROCKS Members Attended: Ray Kent, Sarah Gallagher

II. Request to Committee

The risk assessment team requested consultation with ROCKS members to discuss the toxicity of pymetrozine degradates of concern in drinking water.

III. Background

The Office of Pesticide Programs is currently working on the registration review of the insecticide, pymetrozine. The registrant has submitted additional environmental fate studies since the last risk assessment was performed. As a result, the Environmental Fate and Effects Division (EFED) and the Health Effects Division (HED) needed to determine whether or not the degradates should be included in the drinking water assessment as degradates of concern.

Pymetrozine is currently registered for use on several crop groups or subgroups (1C, 4, 5A, 5B, 8, and 9), as well as on a small number of individual commodities (asparagus, cotton, hops, pecans, and turnip greens). The crops with the highest usage rates are potatoes (41% total lbs a.i.), pecans (16%), lettuce (12%) and cantaloupes (6%). In addition, pymetrozine is registered for use on several non-agricultural commodities: ornamental plants, non-bearing fruit and nut trees in nurseries, and Christmas trees.

HED's Metabolism Assessment Review Committee met on October 4, 1995 and on July 8, 1999, to determine the residues of concern in plants and livestock. The committee decided that the residue of concern for tolerance enforcement was parent pymetrozine. The residues of concern for risk assessment are parent pymetrozine, as well as the plant metabolites GS-23199, CGA-215525, CGA-249257, and CGA-294849. Furthermore, the Committee determined that GS-23199 could serve as a marker compound for CGA-215525, CGA-249257, and CGA-294849. In ruminants, the residues of concern for risk assessment are pymetrozine and the ruminant metabolite CGA-313124. The chemical names and structures of these compounds can be found in Attachment B.

IV. Hazard Considerations

A. Active Ingredient Toxicity:

HED selected acute and chronic dietary endpoints based on results of the rat developmental neurotoxicity study. The endpoint is based on morphometric changes in the brains of female pups on PND 12 and male pups on PND 63. A no observable adverse effect level (NOAEL) was not identified; as a result, the lowest observable adverse effect level (LOAEL) was used for establishing the population adjusted doses. HED reduced the FQPA Safety Factor to 1x. As a result, the acute and chronic population adjusted doses (aPAD and cPAD, respectively) are 0.0081 mg/kg/day. HED classified pymetrozine as a "likely human carcinogen" based on male mouse liver benign hepatoma and/or carcinoma combined tumors. The cancer potency factor is 0.0119 $(mg/kg/day)^{-1}$.

The toxicological endpoints and doses for use in pymetrozine dietary risk assessments are summarized in the following table.

Pymetrozine Toxicological Doses and Endpoints for Dietary Exposure and Risk Assessments.				
Exposure/ Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (All populations including infants and children)	LOAEL = 8.1 mg/kg/day	UF_A= 10x UF_H= 10x UF_L= 10x SF_{FQPA}= 1x	aRfD= 0.0081 mg/kg/day aPAD= 0.008 mg/kg/day	Developmental Neurotoxicity (Rat) LOAEL = 8.1 mg/kg/day, based on morphometric changes in the brains of female pups on PND 12 and male pups on PND 63. [NOAEL not identified]
Chronic Dietary (All populations including infants and children)	LOAEL = 8.1 mg/kg/day	UF_A= 10x UF_H= 10x UF_L= 10x SF_{FQPA}= 1x	cRfD= 0.0081 mg/kg/day cPAD= 0.0081 mg/kg/day	Developmental Neurotoxicity (Rat) LOAEL = 8.1 mg/kg/day, based on morphometric changes in the brains of female pups on PND 12 and male pups on PND 63. [NOAEL not identified]
Cancer	Classification: "likely human carcinogen." A cancer potency factor of 0.0119 $(mg/kg/day)^{-1}$ was calculated for pymetrozine based on male mouse liver benign hepatoma and/or carcinoma combined tumors.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = uncertainty factor for extrapolation from a LOAEL to a NOAEL. FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose.

B. Drinking Water Degradate Toxicity

The registrant did not submit toxicity studies for the pymetrozine drinking water degradates.

C. Structure-Activity Relationship Analyses

HED performed DEREK runs on the degradates in Section VIII, below. Attachment B contains a tabular summary of the results of the runs.

V. Exposure Considerations - Water

EFED's ROCKS briefing memo addresses drinking water exposure considerations (D440305, J. Joyce, 6/1/2017). Major routes of dissipation of pymetrozine in the environment following application include spray drift and runoff on eroded sediment/soil as well as transformation. As a result, pymetrozine might reach surface waters used as source drinking water. Pymetrozine is less likely to be found in groundwater used as source drinking water as it is not expected to leach through the soil profile. However, pymetrozine could reach groundwater in areas with karst soils or where macro particle transport through the soil occurs. A total of twelve pymetrozine transformation products could reach surface water and/or groundwater sourced as drinking water. Three of these transformation products (CGA 359009, CGA 366431, and CGA 363430) retain both the triazine and pyridine moieties, as such, they are structurally similar to parent pymetrozine. The remaining compounds retain either the triazine or pyridine moiety.

Transformation products that contain both the triazine and pyridine moieties

CGA 359009

CGA 359009 was a major transformation product of pymetrozine in three types of studies (soil photolysis, aerobic soil metabolism, and aerobic aquatic metabolism), but generally decline in percent applied radioactivity over time. One aerobic soil study suggests CGA 359009 degrades quicker than parent with a half-life of 2.5 days. In a batch equilibrium study, CGA 359009 was unstable over a 24-hour equilibrium period, but a 4-hour equilibrium period was achieved to assess adsorption/desorption properties. This degradate is more mobile than parent and is classified as moderately mobile (K_{oc} 284 to 436; 1/n = 0.74 –0.86) in soil, based on laboratory batch equilibrium studies. CGA 359009 was not observed to leach beyond the top 6 inches of the soil profile in some terrestrial field dissipation studies, however, it was quantified in lysimeter leachate (0.06%), roughly comparable to depths of 18-24 inches. Based on these data, CGA 359009 may reach surface water and/or groundwater.

CGA 366431

CGA 363431 was a major transformation product in aerobic soil metabolism studies with residues exceeding 10% of applied at study termination (363 days) in one soil study. Based on EPISuite estimates (K_{oc} of 0.3 to 20) this transformation product is expected to be much more mobile than parent; however, the precise estimates are uncertain as EPISuite mobility estimates for parent pymetrozine indicate pymetrozine to be more mobile than batch equilibrium studies indicate. While little data are available to assess the mobility and persistence of CGA 363431 it is possible that it may reach surface water and/or groundwater.

CGA 363430

CGA 363430 was an aerobic soil transformation product observed at a maximum concentration of 9% applied radioactivity, but remained at similar concentrations at study termination (363 days). These concentrations were observed late in the study when sampling intervals are spaced further apart, as such, concentrations may have exceeded 10% of the applied material. Based on EPISuite estimates (K_{oc} of 4 to 63), this transformation product is expected to be much more mobile than parent. Taken together, these data indicate that CGA 363430 may also reach surface water and/or groundwater due to potential persistence and mobility data.

Transformation products that contain only the triazine moiety

CGA 294849

CGA 294849 was observed to form in all environmental fate studies except for hydrolysis. It was only a major transformation product in the aerobic aquatic metabolism study. The quantity of CGA 294849 was found to decrease overtime; it had a maximum percent applied radioactivity of 10%, 14 days into the study, but decreased to 1.4% by study termination (102 days). This degradate is expected to be mobile (K_{oc} of 4 to 10) in soil, based on EPISuite estimated values. In a terrestrial field dissipation study, there was one sample detection of CGA 294849 at 6 to 12 inches below

ground surface. CGA 294849 was also the most prominent transformation product (0.35%) quantified in lysimeter leachate, roughly comparable to depths of 18-24 inches. In summary, CGA 294849 has the potential to reach surface water and/or groundwater.

CGA 215525

CGA 215525 is expected to be formed directly from parent, and was measured at a maximum concentration of 48% and 79% in hydrolysis and aqueous photolysis studies, respectively. Concentrations remained above 30% at study termination in both studies. CGA 215525 was not observed at depths greater than 6 inches in terrestrial field dissipation studies. It is expected to be much more mobile (K_{oc} of 2 to 4) than parent in soil, based on EPISuite estimated values. However, the accuracy of these estimates is uncertain as EPISuite mobility estimates for parent pymetrozine indicate pymetrozine to be more mobile than batch equilibrium studies indicate. Nevertheless, CGA 215525 may also reach surface water and/or groundwater.

Hydroxy CGA 215525

Hydroxy CGA 215525 is also known as 4-amino-4,5-dihydro-5-hydroxy-6-methyl-l,2,4-triazin-3(2H)-one, and SYN 505866, depending on the study in which it was identified. This compound was observed in aquatic photolysis, anaerobic aquatic metabolism, and aerobic soil metabolism studies. In an aquatic photolysis study, Hydroxy CGA 215525 steadily increased in percent applied radioactivity over time to a maximum of 10% at study termination (30 days). It reached a maximum of 20% from an anaerobic aquatic study at study termination. It was also detected in an aerobic soil metabolism study at a maximum of 9%, 15 days into the study, but decreased to non-detect at study termination (120 days). Adsorption and desorption properties of CGA 215525-OH could not be assessed in batch equilibrium because it was unstable in soil after 2 hours of testing. Hydroxy CGA 215525 is expected to be much more mobile than parent based on EPISuite estimates (K_{oc} of 0.15 to 10), however, the accuracy of these estimates is uncertain as EPISuite mobility estimates for parent pymetrozine indicate pymetrozine to be more mobile than batch equilibrium studies indicate. Hydroxy CGA 215525 will likely not be found in surface water or groundwater because although it is likely to be mobile, it does not demonstrate persistence.

VI. Committee/Team Recommendation for Degradates of Concern in Drinking Water

In determining the drinking water degradates of concern, the ROCKS members in attendance relied on the alerts given in the DEREK reports. A summary table of the chemical structures and the results of the reports are provided in Attachment B.

Degradates of Concern

Based on toxicological considerations and the fact that they're major degradates in the environmental fate studies, these are the degradates of concern in drinking water:

Parent pymetrozine
CGA 359009
CGA 366431
CGA 363430 (maximum of 9% in environmental fate studies)

Rationale: The latter three compounds are degradates of concern because they contain both rings and are similar in structure to the parent.

CGA294849
CGA 215525
Hydroxy CGA 215525 (also identified in the environmental fate studies as 4-amino-4,5-dihydro-5-hydroxy-6-methyl-1,2,4-triazin-3(2H)-one, and SYN 505866 (SYN 505866 was 9% AR in the aerobic soil metabolism study only)).

Rationale: These three compounds are of toxicological concern because they contain a hydrazine substructure that might be linked to the toxicity of the parent. For these compounds, the DEREK runs gave the following alert: plausible for carcinogenicity, hepatotoxicity, mutagenicity, teratogenicity, and skin sensitization. HED assumes that these compounds are of equal toxicity to the parent.

Degradates that are Not of Concern

CGA 249257 and GS 23199: These 2 major degradates contain the triazine moiety, but there is no attached nitrogen (no hydrazine substructure). The DEREK runs did not indicate that there would be a cause for toxicological concern.

CGA 180777, CGA 300407, and CGA 255548: These 3 major degradates contain the pyridine ring. One of these is niacin (CGA 180777), which is not of toxicological concern. One of the other pyridine-containing compounds (CGA 300407) is the corresponding aldehyde of niacin (which is an acid) and is likely to be metabolized to niacin in the human body. The other degradate (CGA 255548) is the corresponding hydroxy aldehyde of niacin. The aldehyde substructure of the degradate is likely to be oxidized to a carboxylic acid in the body leading to rapid excretion. In addition, CGA 255548 was only a major degradate in the aerobic soil metabolism study. It reached a maximum %AR of 16% at 24 days and decreased to 1.1% AR at 120 days.

Summary Table

Table 1. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression			
Matrix		Residues Included In Risk Assessment	Residues Included In Tolerance Expression
Plants	Primary Crop	Pymetrozine, GS 23199, CGA 215525, CGA 249257, CGA 294849[1]	Pymetrozine
	Rotational Crop	Not Applicable	Not Applicable
Livestock	Ruminant	Pymetrozine, CGA 313124	Not Applicable
	Poultry	Not Applicable	Not Applicable
Drinking Water		Pymetrozine, CGA 359009, CGA 366431, CGA 363430, CGA 294849, CGA 215525, Hydroxy CGA 215525	Not Applicable

[1] GS 23199 can serve as a marker compound for CGA 215525, CGA 249257, and CGA 294849

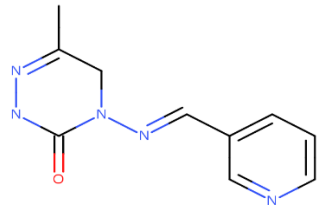
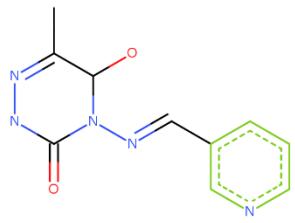
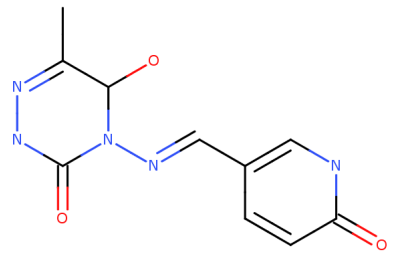
Attachment A. Table of Drinking Water Degradates Found in Rat and Mice Metabolism Studies

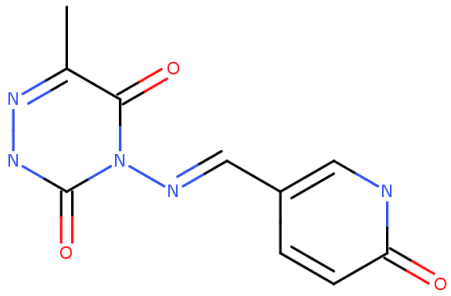
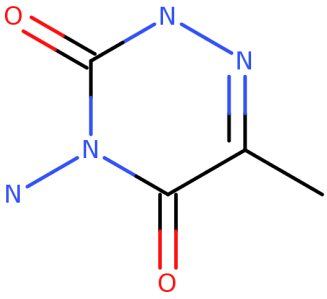
Pymetrozine Degradates of Concern Found in Rat and Mice Metabolism Studies									
			% from Metabolism study (urine)				% from Metabolism study (feces)		
	Metabo-lite[1]	Degradate	Mouse[2]	Rat[2]	Rat[1]		Mouse[2]	Rat[2]	Rat[1]
Contains both Triazine and Pyridine Moieties	1U	Pymetrozine/CGA 215944	5.5-9.6	6-15	2 (low dose; 0.5 mg/kg) 15-22 (high dose; 100 mg/kg)		0.8-3.3	0.5-1.6	0.4-1.1 (high dose; 100 mg/kg)
Contains both Triazine and Pyridine Moieties	2U	CGA 359009	2.8-5.7	9.2-14.4	4-5		0.5-1.7	0.1-0.5	2.2-9.9 (low dose; 0.5 mg/kg) 4.3-9.5 (high dose; 100 mg/kg)
Contains both Triazine and Pyridine Moieties		CGA 366431	--	--	--		--	--	--
Contains both Triazine and Pyridine Moieties		CGA 363430*	--	--	--		--	--	--
Contains Triazine Moiety		CGA 294849	3	3	<1		2	2	<1
Contains Triazine Moiety		CGA 249257	6	--	--		9	5	<1
Contains Triazine Moiety		GS 23199	15	12	<1		3	6	<1
Contains Triazine Moiety		CGA 215525	14	10	<1		8	10	--
Contains Triazine Moiety		Hydroxy CGA 215525	--	--	--		--	--	--
Contains Triazine Moiety		4-amino-4,5-dihydro-5-hydroxy-6-methyl-l,2,4-triazin-3(2H)-one[3]	--	--	--		--	--	--
Contains Triazine Moiety		SYN 505866*	--	--	--		--	--	--
Contains Triazine Moiety		CGA 371075*	--	--	--		--	--	--
Contains Pyridine Moiety	6U	CGA 300407	7	14	4.1-5.4 (high dose; 100 mg/kg)		7	5	--

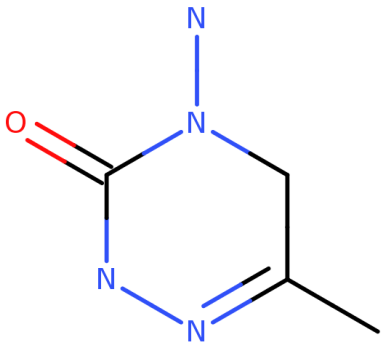
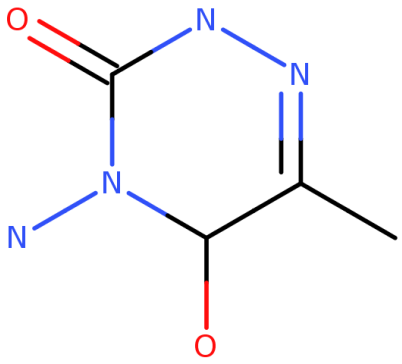
Pymetrozine Degradates of Concern Found in Rat and Mice Metabolism Studies									
			% from Metabolism study (urine)				% from Metabolism study (feces)		
Contains Pyridine Moiety		CGA 255548	--	--	--		--	--	--
Contains Pyridine Moiety		CGA 180777	present[4]	present[4]	<1		15	26	<1
[1]:From MRID 44024957									
[2]: From MRID 44517721									
[3]: May be the same transformation product as SYN 505866									
[4]: combined with 6 other metabolites 28% (mice) 15% (rats)									
*: 9% of applied radioactivity									

Attachment B. DEREK Runs for Pymetrozine Major Drinking Water Degradates

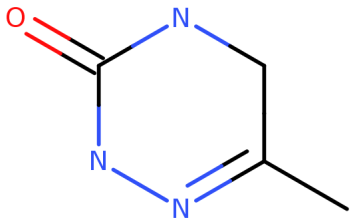
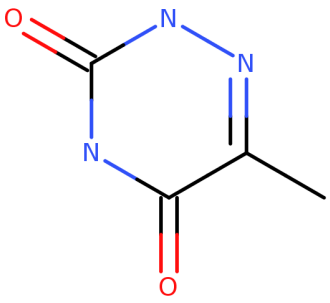
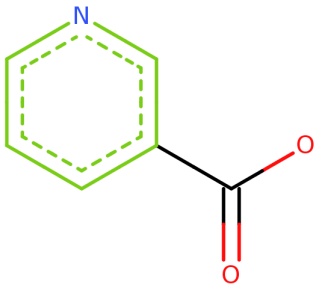
B.1. Degradates that HED has Identified as Being Degradates of Concern

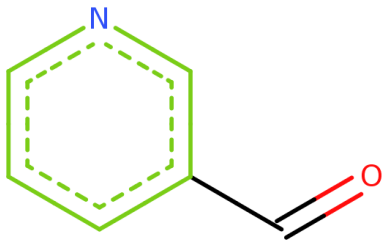
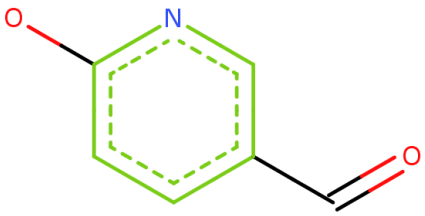
Compound and Structure	Summary of DEREK alerts
Pymetrozine 1,2,4-triazin-3(2H)-one,4,5-dihydro-6-methyl-4-[(3-pyridinylmethylene)amino) 	◆ **Mutagenicity in vitro in bacterium is INACTIVE** • No misclassified or unclassified features ◆ **Skin sensitisation in mammal is PLAUSIBLE** • Alert matched: 448 Hydrazine or precursor
CGA 359009 4,5-dihydro-5-hydroxy-6-methyl-4-[(3-pyridinylmethylene)amino]-1,2,4-triazine-3-(2H)-one 	◆ **Mutagenicity in vitro in bacterium is INACTIVE** • No misclassified or unclassified features ◆ **Skin sensitisation in mammal is PLAUSIBLE** • Alert matched: 448 Hydrazine or precursor
CGA 366431 5-Hydroxy-6-methyl-4-[(6-oxo-1,6-dihydro-pyridine-3-ylmethylene)amino]-4,5-dihydro-2H-[1,2,4]triazine-3-one 	◆ **Mutagenicity in vitro in bacterium is INACTIVE** • No misclassified or unclassified features ◆ **Skin sensitisation in mammal is PLAUSIBLE** • Alert matched: 448 Hydrazine or precursor

CGA 363430 6-methyl-4-[(6-oxo-1,6-dihydro-pyridine-3-ylmethylene)-ammo]-2H-[1,2,4]triazine-3,5-dione 	◆ **Mutagenicity in vitro in bacterium is INACTIVE** • No misclassified or unclassified features ◆ **Skin sensitisation in mammal is PLAUSIBLE** • Alert matched: 448 Hydrazine or precursor
CGA 294849 4-amino-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione 	◆ **Carcinogenicity in mammal is PLAUSIBLE** • Alert matched: 114 Hydrazine ◆ **Hepatotoxicity in mammal is PLAUSIBLE** • Alert matched: 615 Hydrazine ◆ **Mitochondrial dysfunction in mammal is EQUIVOCAL** • Alert matched: RapidPrototype108 Hydrazine ◆ **Mutagenicity in vitro in bacterium is PLAUSIBLE** • Alert matched: 491 N-Amino heterocycle ◆ **Nephrotoxicity in mammal is EQUIVOCAL** • Alert matched: RapidPrototype036 Hydrazine ◆ **Skin sensitisation in mammal is PLAUSIBLE** • Alert matched: 448 Hydrazine or precursor ◆ **Teratogenicity in mammal is PLAUSIBLE** • Alert matched: 605 Hydrazine

CGA 215525 6-methyl-4,5-dihydro-2H-1,2,4-triazin-3-one  	◆ **Carcinogenicity in mammal is PLAUSIBLE** • Alert matched: 114 Hydrazine ◆ **Hepatotoxicity in mammal is PLAUSIBLE** • Alert matched: 615 Hydrazine ◆ **Mitochondrial dysfunction in mammal is EQUIVOCAL** • Alert matched: RapidPrototype108 Hydrazine ◆ **Mutagenicity in vitro in bacterium is PLAUSIBLE** • Alert matched: 491 N-Amino heterocycle ◆ **Nephrotoxicity in mammal is EQUIVOCAL** • Alert matched: RapidPrototype036 Hydrazine ◆ **Skin sensitisation in mammal is PLAUSIBLE** • Alert matched: 448 Hydrazine or precursor ◆ **Teratogenicity in mammal is PLAUSIBLE** • Alert matched: 605 Hydrazine
Hydroxy CGA 215525 SYN 505866 4-amino-4,5-dihydro-5-hydroxy-6-methyl-1,2,4-triazin-3(2H)-one  	◆ **Carcinogenicity in mammal is PLAUSIBLE** • Alert matched: 114 Hydrazine ◆ **Hepatotoxicity in mammal is PLAUSIBLE** • Alert matched: 615 Hydrazine ◆ **Mitochondrial dysfunction in mammal is EQUIVOCAL** • Alert matched: RapidPrototype108 Hydrazine ◆ **Mutagenicity in vitro in bacterium is PLAUSIBLE** • Alert matched: 491 N-Amino heterocycle ◆ **Nephrotoxicity in mammal is EQUIVOCAL** • Alert matched: RapidPrototype036 Hydrazine ◆ **Skin sensitisation in mammal is PLAUSIBLE** • Alert matched: 448 Hydrazine or precursor ◆ **Teratogenicity in mammal is PLAUSIBLE** • Alert matched: 605 Hydrazine

Appendix B.2. Degradates that HED has Identified as Not Being Degradates of Concern

Compound and Structure	Summary of DEREK alerts
CGA 249257 6-methyl-4,5-dihydro-2H-1,2,4-triazin-3-one 	◆ **Mutagenicity in vitro in bacterium is INACTIVE** • No misclassified or unclassified features ◆ **Skin sensitisation in mammal is PLAUSIBLE** • Alert matched: 448 Hydrazine or precursor
GS 23199 6-methyl-2H-1,2,4-triazine-3,5-dione 	◆ **Mutagenicity in vitro in bacterium is INACTIVE** • No misclassified or unclassified features ◆ **Skin sensitisation in mammal is PLAUSIBLE** • Alert matched: 448 Hydrazine or precursor
CGA 180777 (Niacin) Pyridine-e-carboxylic acid 	◆ **Mutagenicity in vitro in bacterium is INACTIVE** • No misclassified or unclassified features

CGA 300407 3-pyridinecarboxaldehyde  	◆ **Hepatotoxicity in mammal is EQUIVOCAL** • Alert matched: RapidPrototype019 Aromatic aldehyde ◆ **Mutagenicity in vitro in bacterium is INACTIVE** • No misclassified or unclassified features
CGA 255548 6-hydroxypyridine-3-carbaldehyde  	◆ **Hepatotoxicity in mammal is EQUIVOCAL (Tautomer 1)** • Alert matched: RapidPrototype019 Aromatic aldehyde ◆ **Mutagenicity in vitro in bacterium is INACTIVE (Tautomer 1)** • No misclassified or unclassified features ◆ **Mutagenicity in vitro in bacterium is PLAUSIBLE (Tautomer 2)** • Alert matched: 302 alpha,beta-Unsaturated aldehyde ◆ **Skin sensitisation in mammal is PLAUSIBLE (Tautomer 2)** • Alert matched: 479 alpha,beta-Unsaturated aldehyde or precursor

Appendix B.3. Structure and Chemical Name for Livestock Metabolite

CGA 313124

6-(Hydroxymethyl)-4-[(E)-3-pyridinylmethyleneamino]-2,5-dihydro-1,2,4-triazin-3-one